Tzu Chi Medical Journal 25 (2013) 47–50

Contents lists available at SciVerse ScienceDirect

Tzu Chi Medical Journal

journal homepage: www.tzuchimedjnl.com

Original Article

Prognostic factors affecting short-term outcome of curative rectal cancer resection

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ARTICLE INFO

Article history:
Received 31 October 2012
Received in revised form
10 December 2012
Accepted 18 January 2013

Keywords:
Adjuvant treatment
Chemoradiotherapy
Prognostic factors
Radical resection
Rectal cancer

ABSTRACT

Objectives: The aim of this study was retrospectively to identify tumor characteristics or any other prognostic factors that influence disease survival after curative rectal cancer resection.
Patients and Methods: The records of 95 patients with Stages I, II, or III rectal cancer (TNM system) seen from August 2008 to June 2012 in one institution were reviewed. The patients underwent radical surgery (abdominoperineal resection or laparoanterior resection with lymph node dissection) as definitive therapy and then adjuvant treatment if pathology indicated T3 or T4 lesions, lymph node involvement, or positive margins. Radiation therapy (54 Gy) was delivered to the gross tumor volume and 45–50 Gy to the nodal region. The chemotherapy protocol consisted of 12 biweekly courses of oxaliplatin (85 mg/m^2), 5-fluorouracil (FU) (400 mg/m^2), and leucovorin (400 mg/m^2) on Day 1, followed by continuous infusion of 5-FU (2400 mg/m^2) for 48 hours.
Results: The 3-year cumulative overall survival rates for Stages I, II, and III rectal cancer were 100%, 100%, and 75%, respectively. Univariate analysis for all 91 patients indicated that pN classification, stage, surgical margin $\leq$ 10 mm, and extracapsular spread (ECS) were significantly associated with overall survival. The pN classification and stage also significantly affected the disease-free survival and distant metastasis-free survival. Furthermore, univariate analysis indicated vascular permeation, neural invasion, and surgical margin $\leq$ 10 mm were significantly associated with disease-free survival. Vascular permeation also significantly affected distant metastasis-free survival. On multivariate analysis for all patients, pN classification and close surgical margin significantly affected disease-free survival.
Conclusion: The presence of lymph node involvement and close margins was associated with lower disease-free survival. More aggressive postoperative therapy is suggested for patients if these factors exist.

1. Introduction

Colorectal cancer is one of the most frequently diagnosed cancers and a major cause of cancer deaths worldwide. The incidence of colorectal cancer is increasing and the condition remains the major cause of death from cancer in Taiwan [1]. Rectal cancer has a high rate of local relapse after surgery alone, with approximately half of recurrences located in the pelvis [2]. The primary treatment for rectal cancer is resection of the primary tumor, and adjuvant treatment is needed in high-risk patients [3]. Adjuvant chemotherapy and radiation therapy have been shown to be effective in reducing or eradicating cancers. In the late 1950s, fluorouracil (5-FU), administered in a bolus, was the chemotherapeutic agent of choice in the management of advanced colorectal carcinoma. Subsequently, 5-FU, of which prolonged exposure leads to increased antitumor activity, was the treatment of choice [4]. Then, postoperative chemoradiotherapy (CCRT) for Stage II and III rectal

Conflict of interest: none.

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1016-3190/$ – see front matter
http://dx.doi.org/10.1016/j.tcmj.2013.01.007

cancer became standard treatment [5]. In recent years, the availability of many new chemotherapy and targeted therapy agents has increased survival in patients with colorectal cancer [6]. Despite the many new agents and modern techniques, local recurrence and distant metastasis remain a challenge, especially in patients with advanced stage disease. Therefore, the aim of this study was to retrospectively determine tumor characteristics or any other prognostic factors that influence survival after curative resection for rectal cancer.

2. Patients and methods

The records of 95 patients with Stage I to III rectal cancer (TNM system) seen from August 2008 to June 2012 in one institution were reviewed. These patients received radical surgery as definitive therapy and then adjuvant CCRT if the pathology report indicated T3 or T4 lesions, lymph node involvement, or positive margins. Four patients were excluded from the analysis because of loss to follow-up (3 patients) or occurrence of a synchronous second primary tumor (1 patient). In all patients, rectal cancer was diagnosed histologically by pathologists and none of these patients had a history of cancer. All patients were informed about their disease treatment, including potential benefits and possible adverse effects, and were treated by multidisciplinary teams of colorectal surgeons, radiation oncologists, medical oncologists, and dieticians.

2.1. Ethics statement

The study followed the Declaration of Helsinki guidelines. The study protocol was approved by the Buddhist Dalin Tzu Chi General Hospital Institutional Review Board (B10102003).

2.2. Treatment

Radical surgery consisted of abdominoperineal resection or laparoanterior resection with lymph node dissection. Pathology reports were reviewed to establish tumor size, grade, type, surgical margins, lymph nodes involved, perineural invasion, vascular permeation, lymphatic permeation, and extracapsular spread (ECS). Subclavian venous-access catheters were placed for nutritional support and administration of chemotherapy. Adjuvant treatments were started 4–6 weeks after surgery. Adjuvant CCRT plus chemotherapy was indicated for T3 lesions, T4 lesions, lymph node involvement, or positive margins.

Radiation therapy was delivered using three-dimensional conformal techniques. The radiation field encompassed the primary tumor bed and pelvic lymph nodes. Treatment was delivered with a 6–10 MV multileaf collimator system (Precise, Elekta, Crawley, UK) using a step-and-shoot method with five coplanar beams. The critical normal structures used for optimization included the bladder and rectum. The treatment plan and dose were verified before treatment; a weekly machine-check film involving electronic portal imaging was performed to ensure setup accuracy during treatment. The prescribed doses delivered by external beam radiation therapy were as follows: 50–54 Gy to the gross tumor volume and 45–50 Gy to the nodal region. Conventional radiation therapy fractionation was given, namely 1.8–2.0 Gy per day and 5 days per week for 6 weeks. Chemotherapy was given concurrently with and after radiation therapy. The chemotherapy protocol consisted of 12 biweekly courses of oxaliplatin (85 mg/m^2), 5-FU (400 mg/m^2), and leucovorin (400 mg/m^2) on Day 1, followed by continuous infusion of 5-FU (2400 mg/m^2) for 48 hours. Treatment was withheld for Grade 3 and 4 toxicity according to the common toxicity criteria of the National Cancer Institute, V2.0 [7].

2.3. Patient follow-up and patterns of failure

Patients were assessed at 3, 6, and 12 months and then every 6–12 months for 5 years; this was done more often if clinically indicated. Survival was calculated from the date of diagnosis to the date of the most recent follow-up, recurrence, or death. The pattern of failure was defined according to the first site of failure. Local failure was defined as recurrence of the primary tumor; locoregional failure, as recurrence of metastasis to the regional lymph nodes; and distant failure, as metastasis to any site beyond the primary tumor and the regional lymph nodes. After recurrence or metastasis, patients received salvage therapy as determined by their physicians.

3. Statistical analysis

Baseline characteristics were analyzed using a *t*-test for continuous variables and a χ^2 test for categorical variables. The Kaplan-Meier method was used for survival analysis [8]. The difference between groups was determined using the log-rank test [9]. Cox proportional hazard regression was used to perform multivariate hazard ratio (HR) analysis. For estimating the effective size, HR was provided with a 95% confidence interval (CI) in addition to a conventional p value. SPSS 12.0 software (SPSS Inc, Chicago, IL, USA) was used for the analysis of all data. A statistically significant difference was defined by $p < 0.05$.

4. Results

The patient characteristics are presented in Table 1. The mean age was 65 years (range, 35–86 years). The median patient follow-up at the commencement of the analysis was 18 months (range, 3–38 months). Of the 21 patients with Stage I disease, 19 patients received surgery alone and two received surgery plus single adjuvant therapy. Of the 39 patients with Stage II disease, five received surgery alone, 26 received surgery plus adjuvant CCRT, and eight

Table 1
Patient characteristics.

Variable	No. of patients	%
Age		
<65 y	38	41.8
≥65 y	53	58.2
Sex		
Male	50	54.9
Female	41	45.1
pT		
1–2	25	27.5
3–4	66	72.5
pN		
0	60	65.9
1–2	31	34.1
pStage		
I	21	23.1
II	39	42.9
III	31	34.1
Extracapsular spread		
Negative	79	86.8
Positive	12	13.2
Lymphatic permeation		
Negative	37	40.7
Positive	54	59.3
Vascular permeation		
Negative	80	87.9
Positive	11	12.1
Neural invasion		
Negative	64	70.3
Positive	27	29.7

pN = node metastasis; pStage = pathologic stage; pT = tumor extent.

received surgery plus single adjuvant therapy. Of the 31 patients with Stage III disease, six received surgery alone, 19 received surgery plus adjuvant CCRT, and six received surgery plus single adjuvant therapy. The radiotherapy dose was 2340–6120 cGy (median, 5040 cGy). Of the 47 patients receiving radiotherapy, 35 received the full planned dose and 12 received an incomplete dose because of treatment-induced complications. Forty-seven of the 59 patients who received chemotherapy completed the full course of chemotherapy and the others received less than 12 cycles at a reduced dose. The 3-year cumulative overall survival rates for Stages I, II, and III were 100%, 100%, and 75%, respectively. The other rates are summarized in Table 2.

Univariate analysis for all 91 patients indicated significant associations of pN classification, stage, surgical margin $\leq$ 10 mm, and ECS with overall survival (Table 2). The pN classification and stage also significantly affected disease-free survival and distant metastasis-free survival. Furthermore, univariate analysis indicated significant associations of vascular permeation, neural invasion, and surgical margin $\leq$ 10 mm with disease-free survival. Vascular permeation also significantly affected distant metastasis-free survival (Table 2). Multivariate analysis for all patients found no significant associations with overall survival. However, pN classification and close surgical margins significantly affected disease-free survival (Table 3) and were the two most significant factors affecting clinical outcome.

Table 3
Significant prognostic factors associated with worse disease-free survival identified by multivariate Cox regression analysis.

Factor	HR	(95% CI)	*p*
Age, y	1.01	(0.91–1.10)	0.74
Sex	0.74	(0.07–8.30)	0.80
pN classification	26.26	(1.52–453.47)	0.02*
Extracapsular spread	0.07	(0.00–3.13)	0.17
Lymphatic permeation	1.84	(0.09–36.40)	0.69
Vascular permeation	4.80	(0.28–83.41)	0.28
Neural invasion	4.24	(0.46–39.28)	0.20
Close surgical margins	21.14	(1.90–234.74)	0.01*

*Statistically significant difference for multivariate analysis ($p < 0.05$).
CI = confidence interval; HR = hazard ratio; pN = node metastasis.

5. Discussion

Patients with rectal cancer are at high risk for local and systemic relapse, especially in the advanced stage [10]. In the current study, pN classification and close margins were the most important outcome predictors in resectable rectal cancer. In addition, a high rate of treatment failure, especially failure at distant sites, was observed in patients with Stage III rectal cancer. Thus, in clinical practice, it is reasonable to treat these patients aggressively.

The most important issue in postoperative treatment is accurate staging, particularly nodal staging. Kim et al [11] reported poorer overall survival in Stage N2 disease than in earlier stages. In addition, the number of involved lymph nodes has been positively correlated with the number of examined lymph nodes [12]. Although there is still no consensus regarding the optimal number of examined lymph nodes, many studies have reported that lymph node ratio provides more useful information to guide adjuvant treatment [13]. In the previous study, nodal status correlated with treatment failure, particularly failure at distant sites. Although treatment strategies for advanced disease have yet to be optimized, more aggressive modalities such as combined targeted therapies should be considered.

Table 2
The 3-year clinical outcomes according to prognostic factors.

Risk factor	3-y overall survival rate (%)	*p*	3-y disease-free survival rate (%)	*p*	3-y local free rate (%)	*p*	3-y distant metastasis -free rate (%)	*p*
Age								
<65 y	80.0	0.61	91.2	0.68	96.3	0.24	91.2	0.94
≥65 y	94.2		91.7		100		93.5	
Sex								
Male	87.2	0.37	93.1	0.90	97.1	0.35	94.9	0.59
Female	97.4		90.7		100		90.7	
pT								
1-2	100	0.22	100	0.12	100	0.53	100	0.15
3-4	89.3		88.5		97.8		89.9	
pN								
0	100	0.003*	98.3	0.005*	100	0.11	98.3	0.015*
1-2	75.0		77.2		94.4		79.8	
pStage								
I	100	0.013*	100	0.019*	100	0.28	100	0.048*
II	100		97.4		100		97.4	
III	75.0		77.2		94.4		79.8	
Extracapsular spread								
Negative	93.8	0.019*	92.0	0.65	98.3	0.77	93.1	0.48
Positive	82.5		91.7		100		91.7	
Lymphatic permeation								
Negative	97.3	0.53	97.3	0.30	100	0.49	100	0.09
Positive	88.8		88.8		97.7		88.8	
Vascular permeation								
Negative	92.6	0.38	93.7	0.047*	98.3	0.77	94.9	0.016*
Positive	88.9		72.7		100		72.7	
Neural invasion								
Negative	93.5	0.21	96.3	0.03*	97.9	0.56	96.3	0.09
Positive	92.3		79.6		100		82.6	
Surgical margins								
≤10 mm	79.7	0.046*	82.1	0.035*	94.7	0.14	85.9	0.12
>10 mm	98.4		94.4		100		94.4	

*Statistically significant difference ($p < 0.05$)
pN = node metastasis; pStage = pathologic stage; pT = tumor extent.

Negative surgical margins are important for local control. However, the association with distal margins is not well established. Nash et al. [14] reported increased risk of mucosal and overall cancer recurrence in patients with close margins after radical surgery. In addition, Komori et al. [15] demonstrated that spread of different pathologic types can be discontinuous. The average lengths of distal spread were 0.5 ± 1.3 mm, 7.0 ± 1.8 mm, 2.7 ± 2.4 mm, and 10.0 ± 9.5 mm for well-differentiated, moderately differentiated, solid-type poorly differentiated, and nonsolid-type poorly differentiated adenocarcinoma, respectively [15]. Recently, Bernstein et al. [16] confirmed that improved local control of rectal cancer could reduce the risk of distant metastases. Therefore, it is important to ensure an adequate surgical distal resection margin. In our study, overall survival differed significantly between patients with surgical margin $\leq$ 10 mm and patients with surgical margin $>$10 mm. In our population, primary radical surgery was suggested for patients with surgical margin $>$10 mm.

ECS, perineural invasion, and lymphatic vascular permeation were common pathology findings in resected rectal cancer. ECS has prognostic value in a variety of cancers, including prostate and head and neck cancers [17,18]. However, only a few pathologic studies have demonstrated a role for ECS in rectal carcinoma. Wind et al. [19] identified ECS as an indicator of particularly aggressive behavior and therefore its prognostic potential, especially in Stage N2 disease. Another study also showed similar results, and that the frequency of distant metastasis was increased in the presence of ECS [20]. In our population, ECS was also an important factor affecting survival. Similar to our report, other reports have identified perineural invasion and lymphatic vascular permeation as potential predictors. Chok et al [21] reported that lymphovascular permeation and perineural invasion significantly increased the risk of lymph node metastasis and were predictive of poorer local control or survival [21]. Importantly, Takahashi et al [22] provided evidence of the beneficial effects of adjuvant therapies in different risk groups. Therefore, modern therapies such as targeted therapies should be considered in the design of different strategies.

Because this is a retrospective study, factors relating to patients and tumor characteristics could not be controlled for, and this may have biased the results. However, the presence of lymph node involvement and close margins were found to be strong prognostic factors associated with disease-free survival. More aggressive postoperative therapy is suggested for patients if these factors exist.

Acknowledgments

This work was supported by the Buddhist Dalin Tzu Chi General Hospital (DTCRD101(2)-I-20).

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